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Rhesus Incompatibility as a Risk Factor for Schizophrenia in Male Adults

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Background: Rhesus (Rh) incompatibility is a cause of hemolytic disease of the fetus and newborn. Hemolytic disease results from the transplacentally transmitted maternal antibodies against Rh factor D and can cause permanent neurological damage in the affected newborn. This study examines the hypothesis that Rh incompatibility may be a risk factor for schizophrenia.

Methods: A sample of 1867 male subjects was divided into two groups, 535 Rh incompatible and 1332 Rh compatible, and compared on rate of schizophrenia.

Results: The rate of schizophrenia was significantly higher in the Rh-incompatible group (2.1%) compared with the Rh-compatible group (0.8%) ($P<.03$). In addition, since the risk for Rh hemolytic disease increases with second and later Rh incompatible pregnancies, it is noteworthy that the second- and later-born incompatible offspring exhibited a significantly higher rate of schizophrenia than second- and later-born compatible offspring ($P<.05$). Also, as predicted, the rate of schizophrenia among firstborn incompatible subjects was not significantly different from that of firstborn compatible subjects (1.1% vs 0.7%).

Conclusion: Rh incompatibility may be a risk factor for schizophrenia.

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MATERNAL infection with influenza during the second trimester of gestation is associated with an increased risk for schizophrenia in the offspring.[1,2] Several independent investigators worldwide have replicated these findings,[3-8] while others have not.[9-12] Influenza viruses elicit autoantibody production in humans and animals.[13-16] Certain autoantibodies of the IgG class cross the placenta and have adverse effects on the developing fetus,[17-19] leading us to consider whether maternal antibodies might cause perturbations in fetal neurodevelopment, in some cases resulting in schizophrenia.

Maternal alloantibodies against the Rhesus (Rh) D antigen are known to result in brain damage in humans secondary to hemolytic disease of the fetus and newborn (HDN). Transplacentally acquired maternal erythrocyte alloantibodies cause fetal erythrolysis in the liver and spleen of the fetus and newborn. In severe cases, death may occur in utero as early as week 18 of gestation as a consequence of hydrops fetalis secondary to profound anemia and associated hypoxia.[20] Post partum, HDN results in an accumulation of bilirubin in the neonate's circulation, which may result in kernicterus (yellow staining of neuronal elements of the brain, including the basal ganglia and hippocampus).[21] Infants who survive kernicterus often suffer from lasting brain damage, manifesting as choreoathetosis, sensorineural hearing deficits, and/or mental retardation.[22]

Rh incompatibility is the most serious cause of HDN. An Rh-negative (d) woman can become immunized to Rh-positive (D) blood through transfusion of D blood, or through miscarriage, abortion, or delivery of an Rh-positive fetus or infant. Hemolytic disease of the fetus and newborn rarely affects firstborn Rh-positive infants, and the incidence and severity of HDN is greater in second- and later-affected neonates.[20,23] In addition, several studies indicate that male fetuses are more likely than female fetuses to initiate maternal Rh D immunization.[24-26]

The neuroanatomical abnormalities

See Methods on next page

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METHODS

SAMPLE SELECTION

The Danish Perinatal Project consists of data on the births of 9182 infants born to 9006 women between 1959 and 1961 at University Hospital in Copenhagen, Denmark. The births of almost all 9182 offspring were observed by senior obstetricians. Extensive data were recorded concerning the pregnancy, including ABO and Rh blood types of 8798 mothers and 3758 infants. A disproportionate amount of serological data from children of Rh-negative mothers was represented (40% vs 17% expected in the Danish population). The selective sampling biased toward offspring of Rh-negative mothers would be expected since these infants were at greatest risk for HDN. One hundred eighty-seven of the 3758 infants with complete serological data died before schizophrenia could develop and an additional 53 subjects were missing data for diagnosis or sex, reducing the sample to 3518 subjects. Other information that was collected included early neurobehavioral and physical examination results, psychiatric diagnoses of both parents, and socioeconomic status.[35]

In 1992 to 1993, the National Psychiatric Register of the Institute for Psychiatric Demography in Risskov, Denmark, was accessed to obtain psychiatric hospital diagnoses of the mothers, fathers, and children in this cohort. This register had its origin in 1938 when systematic registration of patients admitted to mental hospitals in Denmark was begun. It was computerized in 1969 and includes information from all 86 psychiatric institutions in Denmark. The diagnostic system in place at this time was the *International Classification of Diseases, Eighth Revision (ICD-8)*. As of 1994, 50 of the male and 18 of the female offspring were registered as having *ICD-8* diagnoses of schizophrenia. The Rh phenotype is available for 26 of these 68 individuals (21 males and five females). Analyses were limited to male offspring owing to the small number of female offspring with schizophrenia, so the final sample consisted of 1867 male offspring. **Table 1** presents data for the female offspring for the readers' interest.

RISK GROUP CLASSIFICATION

Subjects were divided into Rh-In and Rh-Co groups. The Rh-In group consisted of subjects who were incompatible (Rh-negative mother/Rh-positive offspring—configuration 'd/D') and 110 Rh-positive subjects whose mothers were coded as "mother with known Rh, ABO, or other immunization (configuration imm/D)." In these instances, there was no way to know with certainty the type of immunization. Schizophrenia subsequently developed in two offspring in this category. The reported findings were statistically significant with or without including these two subjects. In addition, since Rh HDN and other types of fetal HDN are fundamentally similar, it is appropriate to include these subjects in the Rh-In group. Therefore, the Rh-In group represents virtually all pregnancies that could give rise to cases of HDN. The Rh-Co group consisted of all pregnancies (d/d, D/D, D/d, imm/d) that could not have given rise to Rh HDN.

STATISTICAL PROCEDURES

χ^2 Tests with continuity correction and two-tailed Fisher's exact test were conducted[36] for hypothesis 1 and hypothesis 2, respectively. Five χ^2 tests with continuity correction and two Fisher's exact tests were conducted for non–hypothesis-driven comparisons of the Rh-In and Rh-Co groups on demographic variables. Logistic regression was conducted to control for differences between the two groups. Three χ^2 tests with continuity correction were conducted comparing the two groups on variables associated with Rh HDN. Since these analyses were hypothesis driven, Bonferroni correction was utilized with a corrected P value of .02.

observed in schizophrenia have been ascribed to perturbations of fetal neurodevelopment, occurring especially during the second trimester.[1,27,28] Consistent with this view, HDN can impair fetal neurodevelopment at this time and may increase the risk for schizophrenia. Furthermore, since *some* of the neuropathological and clinical manifestations of kernicterus parallel those observed for *some* individuals with schizophrenia (ie, disturbed cytoarchitecture of the hippocampus,[29,30] choreoathetosis, and other neuromotor disturbances in infancy and childhood;[31,32] spontaneous abnormal movements in adults;[33] and mental retardation[34]), the postpartum hyperbilirubinemic phase of HDN may also be related to increased risk for schizophrenia.

See also pages 11, 25, and 32

The characteristic features of Rh HDN, which include occurrence only in Rh-incompatible (Rh-In) pregnancies, the tendency for males to initiate maternal Rh D immunization, sparing of firstborn individuals, and greatly increased incidence and severity in second- and later-affected offspring, suggest two hypotheses: (1) the rate of schizophrenia among male offspring from Rh-In pregnancies should be higher than the rate of schizophrenia among male offspring from Rh-compatible (Rh-Co) pregnancies; (2) the rate of schizophrenia among second- or later-born Rh-In offspring should be higher than the rate of schizophrenia among second- or later-born Rh-Co offspring. However, the rate of schizophrenia among firstborn Rh-In offspring should be similar to that among firstborn Rh-Co offspring.

We compared the rate of schizophrenia among offspring from Rh-In and Rh-Co pregnancies in the context of the Danish Perinatal Cohort.[35]

RESULTS

HYPOTHESIS 1

The rate of schizophrenia was found to be 2.1% in the Rh-In group compared with 0.8% in the Rh-Co group (χ^2 [1]=4.73, P=.03; relative risk=2.78, 95% confidence interval=1.2 to 6.6) (Table 1).

Table 1. Rate of Schizophrenia in Adulthood in Rhesus (Rh)-Incompatible and Rh-Compatible Groups

	Total No. of Schizophrenics/Total Sample Size (% With Schizophrenia)			
	Rh Incompatible	Rh Compatible	Total	Significance
Males	11/535 (2.1)	10/1332 (0.8)	**21/1867** (1.1)	.03*
All subjects	12/1062 (1.1)	14/2456 (0.6)	**26/3518** (0.7)	.12*
Females	1/527 (0.2)	4/1124 (0.4)	**5/1651** (0.3)	1.0†

*P value for χ^2.
†P value for Fisher's exact test.

Table 2. Rate of Schizophrenia in Rhesus (Rh)-Incompatible and Rh-Compatible Adult Males by Birth Order

	Total No. of Schizophrenics/Total Sample Size (% With Schizophrenia)			
Birth Order	Rh Incompatible	Rh Compatible	Total	Significance*
Firstborn	2/178 (1.1)	5/672 (0.7)	**7/850** (0.8)	.64
Second born	3/134 (2.2)	2/328 (0.6)	**5/462** (1.1)	.15
Third and later born	4/138 (2.9)	3/306 (0.9)	**7/444** (1.6)	.21
Second and later born	7/272 (2.6)	5/634 (0.8)	**12/906** (1.3)	.05

*P value for Fisher's exact test.

HYPOTHESIS 2

The rate of schizophrenia among second- and later-born Rh-In male offspring was significantly greater (2.6% vs 0.8%) than that of second- and later-born Rh-Co male offspring (Fisher's exact test [two-tailed]: $P=.05$, relative risk=3.32, 95% confidence interval=1.0 to 10.6). In addition, the rate of schizophrenia in firstborn Rh-In and Rh-Co male offspring was 1.1% and 0.7%, respectively. This difference was not significant (Fisher's exact test [two-tailed], $P=.64$) (**Table 2**).

OTHER ANALYSES

Possible confounding influences on our findings include parental diagnosis, age, marital status, number of previous pregnancies, length of gestation, and offspring mortality. No significant differences were observed between the two groups for paternal or maternal diagnosis of schizophrenia. Significant differences were observed in the age, marital status, and number of pregnancies of Rh-In and Rh-Co mothers. Significant differences between the Rh-In and Rh-Co groups were observed for length of gestation and death rate of neonates before the age of 1 year. The significant group differences can be explained as a recruitment bias affecting the subgroup for whom Rh blood group data were available for both mother and offspring. We found that Rh-In mothers were significantly older ($\chi^2[1]=7.73$, $P=.005$), more likely to be married ($\chi^2[1]=7.35$, $P=.007$), and to have more previous pregnancies ($\chi^2[1]=23.69$, $P<.001$) than Rh-Co mothers. Because HDN is confined almost exclusively to second and later pregnancies, mothers at risk of giving birth to offspring with Rh HDN are more likely to be older and married. Rh-Co mothers were more likely than Rh-In mothers to deliver prematurely ($\chi^2[1]=16.78$, $P<.001$) and to have newborns who died in the first year of life ($\chi^2[1]=9.60$, $P=.002$) (**Table 3**).

Logistic regression was conducted to control for the possible confounding influence of these sample differences on the reported findings. The rate of schizophrenia among the Rh-In group remained significantly higher than that of the Rh-Co group when marital status, age, number of pregnancies, and length of gestation were controlled for ($\chi^2[1]=5.90$, $P=.02$).

Since no direct measure of Rh HDN (ie, direct antiglobulin test) in offspring was available for this sample, we examined variables that may be indicative of Rh HDN. These variables included exchange transfusion, bilirubin levels, and jaundice. Exchange transfusions occurred significantly more often for Rh-In than for Rh-Co offspring, 21% and 3.5%, respectively ($\chi^2[1]=258.0$, $P<.001$). Bilirubin levels were available for a subsample, including 319 and 881 subjects in the Rh-In and Rh-Co groups, respectively. Rhesus incompatible subjects were more likely to have critically elevated bilirubin levels (>20 mg/100 mL) than the Rh-Co subjects, 27% vs 19%, respectively ($\chi^2[1]=7.48$, $P=.006$). A subsample of subjects had data reported on the presence of jaundice at the first clinical examination (Rh-In group, n=240; Rh-Co group, n=524). Subjects in the Rh-In subsample were more likely to be reported as having jaundice at the first clinical examination ($\chi^2[1]=20.25$, $P<.001$) than subjects in the Rh-Co subsample (63% vs 45%). The occurrence of exchange transfusions in one fifth of Rh-In subjects, the significantly elevated levels of bilirubin, and the reports of jaundice in a large proportion of Rh-In subjects support our contention that some subjects in the Rh-In group suffered from Rh HDN. Unfortunately, the sample sizes were too small to ascertain whether any of these variables were related to rate of schizophrenia.

COMMENT

Our findings demonstrate that the rate of schizophrenia is increased to 2.1% in male subjects who are Rh-In with their mothers. In contrast, the rate of schizophrenia is 0.8% among those without these characteristics. Also, the rate of schizophrenia is found to be greater in second- and later-born Rh-In offspring than in parity-matched Rh-Co male offspring. Moreover, the rate of schizophrenia is higher in third- or later-born than in second-born Rh-In male offspring (2.9% and 2.2%, respectively) in accordance with the fivefold increase of stillbirths attributed to HDN among second-affected infants. These findings should be considered preliminary as there are several limitations to this study, which will be discussed. We will then speculate on the teratogenic effects of Rh incompatibility that might lead to schizophrenia and conclude with suggestions for future research.

Table 3. Comparison of Rhesus (Rh)-Incompatible and Rh-Compatible Groups on Demographic Variables

Variable, %	Rh Incompatible	Rh Compatible	Significance
Maternal diagnosis of schizophrenia	0.4	0.5	1.0*
Paternal diagnosis of schizophrenia	0.4	0.2	.32*
Maternal age >23 y†	59	52	.005‡
Maternal marital status§	75	68	.007
Parity‖			
Firstborn	39	51	<.001‡
Second born	30	25	
Third born	31	24	
Gestation <38 wk	23	34	<.001‡
Infant mortality	2.9	6.6	.002‡

*P value for Fisher's exact test.
†Median split of total sample.
‡P value for χ^2.
§Percentage who are currently married or were at one time.
‖Offspring included in study by birth order.

LIMITATIONS AND POSSIBLE CONFOUNDS

Limitations of this study include the use of hospital diagnoses, an Rh-Co sample that may be at high risk for other pregnancy and birth complications (PBCs), and a small number of schizophrenic subjects.

The reliability and validity of hospital diagnoses has been questioned. We argue that Danish hospital diagnoses tend to be conservative relative to experienced clinicians' interview diagnoses. Therefore, subjects given a hospital diagnosis of schizophrenia would almost always be diagnosed as schizophrenic during a more detailed clinical interview.[37,38] Furthermore, if errors in diagnostic typing occurred, it is unlikely that they would be more prevalent among Rh-In than among Rh-Co offspring.

The data for subjects in this sample were gathered for research purposes. However, certain medical procedures (such as taking a blood sample from the neonate) were not routine. As a result, this study consisted of a somewhat biased sample toward pregnancies that warranted serological examination.

In future studies, the rate of schizophrenia among female Rh-In offspring must be examined. The disproportionate number of male schizophrenic subjects in our sample is explained by differences in the age at onset between males and females and the age of the subjects when they were checked in the psychiatric register (32 years).[39-41] In addition to age-at-onset differences, the sexes may be differentially susceptible to gestational environmental factors. Therefore, analyzing the sexes separately may provide important information regarding Rh incompatibility as a risk factor for schizophrenia.

HOW MIGHT Rh INCOMPATIBILITY INCREASE THE RISK FOR SCHIZOPHRENIA?

Again, Rh incompatibility is the most serious cause of HDN. We suggest that the fetal hypoxia resulting from hemolysis in Rh HDN may have deleterious effects on fetal neurodevelopment, increasing the vulnerability for schizophrenia later in life. McNeil[42] suggests that prenatal, perinatal, and neonatal oxygen deprivation may increase the risk for schizophrenia. One brain region particularly vulnerable to hypoxia is the hippocampus.[21,43] Neuropathological studies have implicated the hippocampus as a brain region frequently found to be abnormal among schizophrenics.[44] The migration of neurons into the hippocampus is reaching a peak during the second trimester,[45] at which time the transfer of maternal antibodies to the fetus is under way.[46] Furthermore, a study from our laboratory,[1] which has been replicated several times, implicates the second trimester of gestation as critical in the development of schizophrenia.

Second, we proposed earlier that kernicterus at birth may be related to risk for schizophrenia in adulthood. The hyperbilirubinemic phase of postpartum Rh HDN can cause damage to the basal ganglia and hippocampus, brain areas associated with schizophrenia. In addition, some of the clinical manifestations of kernicterus are also observed in preschizophrenics and in adults with schizophrenia. However, given the mounting evidence of second-trimester perturbation in schizophrenia, we suggest that the *fetal* phase of Rh HDN rather than the neonatal phase may be the more critical period of insult. Furthermore, in this study, 19% of the Rh-Co group evidenced critically elevated bilirubin levels. Although the percentage was significantly less than in the Rh-In group (27%), the disparity is not all that great.

Both neuropathology studies and the second-trimester findings are consistent with the hypothesis that the maternal transfer of anti-D antibodies into a Rh-positive fetus, causing HDN (and the concomitant hypoxia and hyperbilirubinemia), may damage brain tissues associated with an increased risk for schizophrenia. Our findings of an increased rate of schizophrenia among Rh-In offspring, those who are at highest risk for Rh HDN, support this hypothesis.

SUGGESTIONS FOR FUTURE RESEARCH

Population prevalence of the d phenotype, information on the heterozygosity or homozygosity of the father's blood type, effects of parity, and the administration of anti-D prophylaxis must be considered in replication attempts. In addition, the presence of PBCs secondary to Rh HDN and their relationship to schizophrenia in adulthood must be further explored.

- The prevalence of the d phenotype ranges from 0% in a Thai population[47] to 20% to 40% in the Basque people.[48] The variance observed in the prevalence of D and d phenotypes worldwide raises the question as to whether populations with increased incidence of Rh incompatibility will also evidence an increased incidence of schizophrenia? To our knowledge, unusual rates of schizophrenia have not been observed in the above-mentioned regions.
- The homozygosity or heterozygosity of the paternal D factor may influence results. All offspring of homozygous D (DD) fathers and d (dd) mothers will be D (Dd), which will increase the probability of anti-D antibody production by the mother's immune system, thereby increasing the probability of HDN.[20]

- Replications must also consider the effect of parity. Nonfirstborn children will have the greatest probability of suffering from HDN,[20] and according to our hypothesis these trends will be evident as a correspondingly increased risk for schizophrenia throughout second and later Rh-In pregnancies.
- Rh HDN has been significantly reduced since the development of anti-D prophylaxis in the late 1960s.[29] Schizophrenia has also been reported to be on the decline. However, the decline has mainly been attributed to changes in both diagnostic practices and economic and social forces.[49] Replication attempts must include samples that predate the administration of anti-D prophylaxis.
- A relationship between PBCs and schizophrenia has been reported.[42,50] A relationship has also been observed for certain PBCs and HDN, such as asphyxia at delivery, pulmonary edema, and other respiratory difficulties.[51] The question arises as to whether PBCs themselves increase the risk for schizophrenia, whether the PBCs merely reflect manifestations of pathological processes occurring earlier in pregnancy that increase the risk for schizophrenia, or a combination of the two.
- These findings may also be relevant to the genetics of schizophrenia. The d genotype is inheritable and will cluster in families; therefore, so, too, will Rh-In pregnancies. If Rh incompatibility is a risk factor for schizophrenia, then schizophrenia would also tend to cluster in these families. These families might mistakenly be identified as having a genetic predisposition for schizophrenia, when in fact they may simply have a genetic predisposition for HDN.

CONCLUSION

This study implicates Rh incompatibility as a risk factor for schizophrenia, a risk factor that involves genetics, maternal immune functioning, PBCs, and fetal neurodevelopment. There are numerous ways in which the hypotheses discussed in this study can be tested. Attempts at replications using other perinatal cohorts are already under way. In addition, retrospective studies examining the psychiatric outcomes of adult survivors of HDN and kernicterus can be designed. Studies examining the rate of Rh incompatibility in large samples of schizophrenic subjects is another possible design. Other forms of fetal/maternal incompatibilities (ie, ABO incompatibility—maternal blood type O, offspring A, B, or AB) and their relationship to schizophrenia can be examined. Studies can be conducted that examine other human hemolytic conditions such as autoimmune hemolytic anemia. Research using animal models can explore the role of hemolysis, consequent hypoxia, and hyperbilirubinemia on fetal neurodevelopment and aberrant behavior. In future studies, the limitations discussed earlier can certainly be overcome through research design. Finally, the observations presented in this study may provide supportive evidence that maternal antibodies can perturb fetal neurodevelopment either through secondary obstetric complications or some other unknown mechanism, causing schizophrenia later in life. Therefore, a wider consideration of the possible role of maternal antibodies and other immune factors in the pathogenesis of schizophrenia is indicated.

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